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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 012004

Application Number: 09/398,610
Filing Date: September 17, 1999
Appellant(s): Edge

Byron V. Olsen

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/23/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-30 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

US Patent No. 5,959,171 Hyttinen et al. 9/28/99

Rybak et al. " Humanization of immunotoxins " Proc. Natl. Acad. Sci. USA, Vol. 89 (1992) pp. 3365-3369.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-8, 10-14, and 16-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,959,171, 9/28/99, filed on 8/17/94, hereafter referred to as Hyttinen et al., in view of Rybak et al. (1992) Proc. Natl. Acad. Sci. USA, Vol. 89, 3165-3169. This rejection is set forth below and in prior Office actions mailed on 6/17/02 and 1/7/03.

Please note that the claims on appeal are subject to an election of species requirement, see the office action mailed on 12/19/00. In the response received from the appellants dated 6/22/01, the appellants elected without traverse the species "fusion proteins comprising angiogenin" for examination on the merits. Claims 8 and 30 are limited to the elected subject matter of a fusion protein comprising angiogenin. Claims 1-7, 10-14, 16-29, and 31-35, however, are still generic and have not been amended to reflect the elected subject matter. All pending claims, including generic claims 1-7, 10-14, 16-29, and 31-35, have been examined **only** to the extent that they read on the elected subject matter.

The applicant claims a transgenic non-human mammal which includes a transgene which comprises a mammary epithelial specific promoter, nucleotide sequence which encodes a signal sequence that directs the secretion of a fusion protein, and a nucleotide sequence which encodes

a fusion protein that comprises a first member and a second member, the second member is an enzyme produced in the milk of a transgenic mammal in biologically active from, and the fusion protein is produced in the milk of the transgenic mamma at a concentration of about 0.1 mg/ml. Again, please note that the elected species under examination is a fusion protein wherein the second member is angiogenin. The applicant further claims methods of making a fusion protein comprising providing said transgenic non-human mammal described above, and allowing the transgene to be expressed. The applicant also claims said methods and transgenic non-human mammals wherein the first member of the fusion protein comprises a subunit of an Ig specific for a tumor antigen selected from a group which includes transferrin receptor.

Hyttinen et al. teaches vectors encoding a fusion protein which comprises a biologically active protein operatively linked to regulatory elements needed for high level mammary gland specific expression derived from a milk protein gene or a mammary tumor virus and a DNA sequence encoding a signal sequence needed for secretion and maturation of the fusion protein (Hyttinen et al., column 3, particularly lines 15-54). Hyttinen et al. also teaches transgenic animals, including cows and goats, made using said vectors, and methods of making a bioactive fusion protein comprising collecting milk from a transgenic mammal which expresses a fusion protein in its milk, and isolating the recombinant fusion protein from the milk (Hyttinen et al., column 3, lines 15-61, and column 5, lines). Hyttinen et al. teaches that the fusion protein has a formula selected from a group which includes R2L-R1 and R3-L-R1, where R2 is a milk-specific polypeptide, R3 is a non-milk polypeptide, L in a linker, and R1 is a desired biologically active polypeptide such as an enzyme (Hyttinen et al. , columns 3-4 bridging paragraph). Regarding the biologically active protein, Hyttinen states that , "The biologically active protein shall be

understood to cover any potent polypeptide that in its free form could cause adverse effects in the producing mammal. Such polypeptides are for example ... enzymes and the like" (Hyttinen et al., column 4, lines 3-10). In one exemplified embodiment, Hyttinen et al. teaches making and using a transgenic mammal which expresses a beta-lactoglobulin-hEPO fusion protein at concentrations of 0.2-1 mg/ml in the transgenic milk (Hyttinen et al., column 10, lines 30-35). Please note that hEPO is an enzyme.

Hyttinen also teaches that the general idea of making and using transgenic bioreactors for the production of large quantities of proteins, particularly human proteins, was suggested as early as 1986 and that numerous examples of transgenic bioreactors exist in the art, citing references from 1991-1992 (Hyttinen et al., column 1). Thus, Hyttinen establishes that at the time of filing, the state of the art of making transgenic mammals which secrete biologically active proteins in the milk was high, and that the prior art recognized the advantages of producing large quantities of biologically relevant, therapeutic proteins in milk of transgenic animals.

Although Hyttinen et al. teaches general methods for making transgenic animals comprising enzyme fusion proteins and methods of making and isolating fusion proteins from the milk of transgenic mammals, Hyttinen et al. differs from the instant invention by not specifically teaching the production of a fusion protein comprising angiogenin. Rybak et al. supplements Hyttinen et al. by teaching nucleic acid expression constructs which encode a secretable fusion protein comprising a single chain antibody against the human transferrin receptor and angiogenin (Rybak et al., abstract). Rybak et al. also teaches that the isolated fusion proteins are capable of inhibiting protein synthesis in human tumor cell lines (Rybak et al., page 3165). While Rybak et al. teaches the expression of the fusion protein in mammalian cell lines

in vitro, the skilled artisan would have been motivated to express the fusion protein taught by Rybak et al. using a mammalian bioreactor system in order to produce larger quantities of the human fusion protein as taught by Hyttinen et al. Therefore, in view of the benefits of using a transgenic bioreactor to produce large quantities of a protein for use in humans as taught by Hyttinen et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to express the fusion protein comprising angiogenin taught by Rybak et al. using the transgenic bioreactors taught by Hyttinen. Further, based on successful use of transgenic bioreactors in expressing large quantities of a variety of human proteins and enzyme containing fusion proteins as taught by Hyttinen et al., the skilled artisan would have had a reasonable expectation of success in expressing the fusion protein comprising the a single chain antibody against the transferrin receptor and angiogenin in the milk of a transgenic mammal according to the methods taught by Hyttinen et al.

(11) Response to Argument

Appellant's arguments have been addressed in the order in which they have been presented in the appellant's appeal brief.

The appellant argues in section I on page 8 of the appeal brief, that the Office has not met the standard for obviousness set forth in *Graham v. John Deere Company* 383 U.S. 1, 17, 148 USPQ 459,467 (1966). The appellant has provided three sets of arguments in support of this position. It is noted that these arguments address each cited reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, these arguments are addressed in order below.

First, under subsection A. on page 9 of the appeal brief, the appellant argues that Hyttinen et al. teaches away from the claimed invention. According to the appellants, the current claims focus on transgenic animals that express active enzymes, whereas Hyttinen et al. teaches away from the claimed invention by using transgenic animals to produce inactive molecules. The appellants argue that the Hyttinen et al. reference does not teach or suggest producing a fusion protein which includes an enzyme in active form, since Hyttinen et al. teaches that the expression of enzymes in transgenic bioreactors can cause severe side effects. In response, the Office has clearly pointed out in the Office Actions mailed on 6/17/02 and 1/7/03 that Hyttinen et al. teaches fusion proteins comprising potent polypeptide such as enzymes which are biologically less active than the free form of the enzyme (Hyttinen et al., column 2, lines 39-42, and columns 3-4). While the fusion proteins described by Hyttinen et al. may not demonstrate 100% of the activity of the free wild type enzyme, a less active enzyme still equates to a "biologically active" enzyme as required by the instant claims as written. The appellants are reminded that the claims on appeal do not recite any specific level of activity, nor does the specification as filed define the phrase "biologically active form" as meaning that the enzyme present in the form of a fusion protein has 100% of the enzymatic activity as the enzyme in its free form. The phrase "biologically active form" is very broad and reads on a fusion protein where the enzyme portion has any level of biological activity. Hyttinen et al. clearly teaches that in one embodiment of the invention the fusion protein comprising an enzyme does in fact have biological activity. Further,

while the appellants argue that the claimed invention requires that the first member does not reduce the activity of the second member of the fusion protein, the claims on appeal do not in fact contain any such limitation. In determining patentability, claims are to be given their broadest reasonable interpretations, and limitations are not to be read into claims from the specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In regards to appellant's assertion that Hyttinen et al. constitutes a failed experiment on its own terms, it is respectfully suggested that the appellants have misunderstood the intent of the teachings present in Hyttinen. Hyttinen clearly sets forth the purpose of their invention which is to offer a practically applicable alternative to mammalian tissue culture systems for the production of "potent" polypeptides which minimizing potential side effects from the expression of these polypeptides in the mammal by 1) using a mammary gland specific expression system that directs the produced fusion protein into the milk and 2) producing the "potent" polypeptides as fusion proteins. Column 2, lines 50-54, of Hyttinen et al. state, " One object of the present invention is to provide a process for the production and secretion of a biologically active polypeptide as a fusion protein into the milk of a mammal without causing to said mammal severe side effects associated with ectopic expression or leakage of said polypeptide". The working example described by Hyttinen et al. in fact presents a fully successful example of their invention. The transgenic mice described in column 10 of Hyttinen express the beta-lactoglobulin-hEPO fusion protein in their milk at high concentration (0.2-1 mg/ml) and are healthy (Hyttinen et al., column 10, lines 30-38). The fact that one of the mice had a slightly elevated hematocrit, while still considered healthy, simply proves that the fusion protein was in fact biologically active. Further, Hyttinen et al. compares transgenic mice which express hEPO

in its native form, versus transgenic mice which express hEPO in a fusion protein and clearly shows that the problems with expression of large quantities of hEPO seen in the non-fusion protein mice, i.e. strongly elevated hematocrit levels and polycytemia leading to early death were not seen in the transgenic fusion protein mice. Thus, the working example in Hyttinen et al. is a clear success. As such, the appellants reliance on *W.L. Gore & Assocs. v. Garlock, United Sates v Adams,* and *In re Wilder* is misplaced. The cited case law concerns inoperative inventions or failed experiments. Hyttinen et al. is neither an inoperative invention or a failed experiment. The invention of Hyttinen et al. was successfully exemplified and as such clearly constitutes appropriate prior art in the context of 35 U.S.C. 103(a). Therefore, for the reasons discussed in detail above, appellant's arguments concerning the teachings of Hyttinen et al. have not been found persuasive.

Appellant's second argument, under subsection B. on page 12 of the appeal brief, states that despite the high standard of skill in the art of transgenic animal systems, there is a clear lack of any teaching in any analogous art of applying solutions for the expression of immuno-fusion proteins in transgenic mammal expression systems and no one in the industry other than the appellants has approached the problem of utilizing transgenic animal expression systems for the production of immuno-fusion proteins in milk. In response, the Office respectfully disagrees with the appellants. It is the position of the office that the teachings of Hyttinen et al. are clearly analogous to the claimed invention, and that Hyttinen et al. has in fact already solved the problem identified by the applicants regarding the expression of enzymes in the milk of transgenic mammals (see columns 2-4, and Example 3 in columns 9-10 of Hyttinen et al.). The previous paragraph provides a detailed discussion of the teachings of Hyttinen et al. as they

relate to the instant invention as claimed. Thus, for reasons stated above, appellant's argument has not been found persuasive.

Appellant's third argument, under subsection C. on page 13, states that Rybak is not an appropriate reference and does not fall within the scope of the applicable prior art. As a first issue, the appellant's appeal brief on page 13 at the bottom contains the sentence, "The Examiner concedes that Hyttinen does not disclose and is in fact silent with regard to:" followed by what appears to be an excerpt from an Office communication. However, the indented text does **not** come from the rejection of record which was first presented in the Office action mailed on 6/17/02 on pages 3-6, or any other communication from the Examiner mailed to the applicants. The examiner of record has **never** conceded that Hyttinen does not teach the expression of biologically active fusion proteins in a transgenic animal. In fact, the examiner of record has made just the opposite point. The teachings of Hyttinen et al. have been disclosed in detail above and it is clearly the Office's position that Hyttinen et al. provides substantial teachings for making transgenic mammals whose cells comprise an expression vector which encodes a fusion protein that comprises an enzyme and for using the transgenic mammal to produce the fusion protein comprising an enzyme in the mammal's milk. Rybak et al. has been cited to supplement the teachings of Hyttinen et al. regarding a specific fusion protein which comprises an immunoglobulin which recognizes transferrin and the enzyme angiogenin.

It appears to be the appellant's position that Rybak does not constitute analogous art because Rybak teaches an *in vitro* system of producing a fusion protein rather than a transgenic system. In response, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which

the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Rybak et al. teaches the production of a fusion protein comprising an immunoglobulin which recognizes transferrin and angiogenin in a mammalian tissue culture system *in vitro*. The fusion protein taught by Rybak et al. is identical to the preferred embodiment of appellant's invention as disclosed in the specification, and broadly claimed in the claims on appeal. Thus, Rybak et al. is clearly pertinent to the particular protein with which the appellant is concerned and is further clearly in the appellant's field of endeavor. The appellant's argument that Rybak et al. cannot be analogous because they do not specifically teach transgenic mice for the production of the fusion protein ignores the fact that the rejection of record is based on the combined teachings of two references, Hyttinen et al. and Rybak et al. As noted above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hyttinen et al., discussed in detail above, provides substantial teachings for the production of fusion proteins comprising enzymes in transgenic mammals and further provides motivation for making fusion proteins in transgenic bioreactors over making fusion proteins in mammalian tissue culture based on the art recognized superiority of transgenic bioreactors for making large quantities of protein in mammalian milk. Rybak et al. teaches mammalian cells which comprise a nucleic acid expression construct which encodes a secretable fusion protein comprising a single chain antibody against the human transferrin receptor and angiogenin, and the production of the fusion proteins in these cells in tissue culture *in vitro* (Rybak et al., abstract). Rybak et al. also provides motivation of making this particular fusion

protein by teaching that the isolated fusion proteins are capable of inhibiting protein synthesis in human tumor cell lines (Rybak et al., page 3165). The fact that Rybak et al. does not suggest using a transgenic bioreactor to produce the fusion protein is irrelevant since Hyttinen et al. has been cited for this teaching and for the motivation to use transgenic bioreactors over mammalian tissue culture to produce large quantities of protein. The applicant's are reminded that for the purpose of combining references under 35 U.S.C. 103(a), the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Further, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988).

In regards to the discussion on page 15 of the Appeal Brief which states that Rybak teaches an *E. coli* system for expression of the fusion protein, this is incorrect. Rybak does **not** teach the expression of the fusion protein in *E. coli*. The entire Rybak et al. reference teaches the production of the fusion protein in mammalian cells. In particular, the appellant is pointed to the materials section on page 3165 which states that the E12B5 cell line is a transfectoma, and the bridging paragraph from pages 3166-3167 which states that the E12B5 cell line was transfected with the mammalian expression plasmid pSVgpt-CH2-ANG. Thus, appellant's comments regarding *E. coli* based expression are inaccurate and moot in view of the actual teachings of Rybak et al. Appellant's reliance on *Wang Laboratories, Inc. v. Toshiba Corp.*, *In re Clay*, *King Instrument Corp. v. Otari Corp.*, and *Union Carbide Corp. v. American Can Co.* are therefore misplaced as well. As stated above, Rybak et al. is clearly pertinent to the particular

protein with which the appellant is concerned and is further clearly in the appellant's field of endeavor since Rybak et al. teaches the production of a fusion protein comprising an immunoglobulin which recognizes transferrin and angiogenin in a **mammalian** tissue culture system *in vitro* and since the fusion protein taught by Rybak et al. is identical to the preferred embodiment of appellant's invention as disclosed in the specification, and broadly claimed in the claims on appeal. Further, Rybak et al. clearly teaches production of the fusion protein in **mammalian** not prokaryotic cells. There is nothing alien or non-analogous about the production of a fusion protein in mammalian cells *in vitro*, and the production of the same fusion protein in mammalian cells *in vivo*, particularly in light of the teachings of Hyttinen et al. which provides substantial motivation for producing fusion protein in the milk of transgenic mammals rather than in mammalian tissue culture in order to produce substantially greater amounts of the desired fusion protein. Therefore, for the reasons discussed in detail above, appellant's arguments regarding Rybak et al. have not been found persuasive.

Returning to appellant's original argument at the start of section I, the appellant's arguments under subsections A-C have not demonstrated that the Office has not met the standards for obviousness set forth in *Graham v. John Deere Company.* The Office action mailed on 6/17/03 followed the guidelines established in *Graham v. John Deere Company.* The rejection of record, presented in full in previous section of this Examiner's Answer, clearly identifies the scope and contents of the prior art, ascertains and sets forth the differences between the prior art and the claims at issue, identifies the level of ordinary skill in the pertinent art, and takes into consideration objective evidence present in the application indicating obviousness or nonobviousness.

In section II, the appellant puts forth the argument that the instant invention satisfies a long felt need in the art, and as such is non-obviousness over the prior art of record, citing *Uniroyal, Inc. v. Rudkin-Wiley Corp.* In support of this argument, the appellant states that they have attached two post-filing abstracts by Frankel et al., and Nagy et al. It is noted for the record that the papers filed on 10/23/03 did not contain any such references or abstracts. Therefore, the relevance of the teachings of Frankel et al. and Nagy et al. cannot be determined. In addition, the appellant is reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c). Further, the Office submits that Hyttinen et al. already recognized the long standing need in the art for reliable expression systems for producing fusion proteins comprising enzymes and provided a successful solution to this problem in the form of transgenic mammals which express the fusion protein in a less active form in the mammal's milk. Thus, appellant's arguments have not been found persuasive in overcoming the instant grounds of rejection.

In section III, the appellant argues that the examiner has failed to establish a case of *prima facie* obviousness based on the teachings of Hyttinen and Rybak, citing *In re Oetiker* and *In re Rijckaert*. In support of this argument, the appellant reiterates the alleged failings of the Hyttinen et al. and Rybak et al. references. These arguments have been addressed in detail above,

see the responses to appellants arguments presented in sections I and II, and have been found unpersuasive. As noted above in response to the appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further in response to applicant's argument that there is no suggestion to combine the references in either Hyttinen et al. or Rybak et al., the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The appellant is reminded that for the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In this case, Hyttinen et al. has been cited as providing motivation for using transgenic bioreactors to produce fusion proteins which comprise an enzyme. The appellant argues that Hyttinen provides no suggestion that a protein secreted at low levels in cell culture could be produced in milk at a level of at least 0.1 mg/ml or that a fusion protein that does not comprise a milk protein would be expressed at high levels in milk, and states that the expression of an immuno-toxin fusion protein at levels greater than 0.1 mg/ml in the milk of transgenic mammals is an "unexpected result" of the claimed invention. In response, the appellant is again reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c). In addition, Hyttinen et al. provides a specific example which demonstrates the expression of a fusion protein comprising beta-lactoglobulin and hEPO in the milk of transgenic mammals at levels between 0.2-1mg/ml, and a separate example which demonstrates that a non-milk protein, hEPO, is also secreted at concentrations of greater than 0.1 mg/ml in transgenic milk (Hyttinen et al., see examples 1 and 3). Hyttinen et al. further establishes in column 1, lines 19-33, that a high level of skill in the art of making transgenic mammals which produce a desired protein in their milk existed as early as 1991, and that the state of the art of transgenic bioreactors was such that the skilled artisan would have had reasonable expectation of success in producing a transgenic mammal which "secrete large amounts of recombinant proteins constitutively into milk during lactation" (Hyttinen et al., column 1, lines 31-33 in particular). It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel,* 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Therefore, based on the high level of skill in the art of making transgenic mammals which secrete large amounts of recombinant protein in their milk, the high level of skill in the art of molecular biology, and the successful demonstration by Hyttinen of transgenic mammals which expresses between 0.2-

1mg/ml of a fusion protein comprising an enzyme in the milk and the expression of greater than 0.1 mg/ml of a non-milk protein in milk, the skilled artisan would have had a reasonable expectation of success in expressing the fusion protein taught by Rybak et al. in large amounts in milk using the transgenic bioreactor system taught by Hyttinen et al. The appellant is reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

The appellant further cites several Court decisions which the appellant's feel support their position that the cited references do not support an obviousness rejection under 35 U.S.C. 103(a). Regarding *Carella v. Starlight Archery* and *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, the instant case differs from the facts in *Carella* or *Yamanouchi Pharm. Co.* in that Hyttinen et al. broadly teaches a system for producing fusion proteins comprising enzymes identical to that recited in the broadest instant claims. Hyttinen et al. has not been applied as a reference under 35 U.S.C. 102 because the instant claims on appeal are subject to a restriction/election requirement. As noted above, the appellant has elected the species of fusion proteins which comprise as a second member angiogenin. Since Hyttinen et al. does not teach the specific embodiment of angiogenin, Rybak was supplied to supplement Hyttinen et al. by teaching mammalian cells which secrete a fusion protein which comprises an immunoglobulin that recognizes transferrin and angiogenin. Thus, all of the elements of the instant claims are clearly taught by Hyttinen et al. or Rybak et al. Motivation for using the transgenic bioreactor system taught by Hyttinen et al. to make the fusion protein taught by Rybak et al. is supplied by the teachings of Hyttinen et al. that transgenic mammals are capable of secreting large amounts

of biologically active proteins in milk as compared to mammalian tissue culture and that the art recognized the superiority of the transgenic bioreactor system for preparing large amounts of protein as early as 1991. Regarding *Cuno Eng'g Corp. v. Automatic Devices Corp.*, the Office has not applied the "flash of genius" requirement for patentability. The Office has applied the standard for establishing obviousness under 35 U.S.C. 103(a) as set forth by *Graham v. John Deere Company.* Regarding *In re Dillon* and *In re Fine* and appellants argument that the rejection rests on improper hindsight, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In regards to appellant's statement that the examiner has stated that the instant claims are "as a whole .. *prima facie* obvious", the examiner of record has never made any statement using the word "as a whole". On page 5 of the Office action mailed on 6/17/02, the page cited by the appellants, the examiner stated, " Therefore, in view of the benefits of using a transgenic bioreactor to produce large quantities of a protein for use in humans, it would have been prima facie obvious to the skilled artisan to express the fusion protein taught by Rybak et al. using the transgenic bioreactors taught by Hyttinen". Therefore, in view of the fact pattern of the instant case, the case law cited by the appellants and appellant's arguments are not compelling and do not overcome the rejection of record.

In conclusion, the Office has properly applied the test for obviousness set forth in *Graham v. John Deere Company* and established a *prima facie* case of obviousness over the claims on appeal based on the teachings of Hyttinen et al. in view of Rybak et al.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

Anne Marie S. Wehbé, Ph.D.
Primary Examiner
AU 1632

January 21, 2004

Conferees

Deborah Reynolds

Amy Nelson

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